Disruption of 5-HT\textsubscript{7} receptors accelerates age-related episodic-like memory decline

Beaudet G., Brehin M., Freret T., Nee G., Delaunay V., Boulouard M., Païzanis E.
Normandie Univ, France
UCBN, GMPc, EA 4259, F-14032 Caen, France
Corresponding author: gregory.beaudet@unicaen.fr

Introduction

Increasing incidence of cognitive impairments related to population ageing is a major public health challenge. In order to identify new therapeutic targets, modulation of serotonergic 5-HT\textsubscript{7} receptors (5-HT\textsubscript{7}R) could be an innovative approach since:

1. gene expression of 5-HT\textsubscript{7}R early decreases during senescence in rats,
2. synaptic plasticity of the hippocampus is altered in 5-HT\textsubscript{7}R knocked-out (KO) mice,
3. pharmacological modulation of 5-HT\textsubscript{7}R improves episodic-like memory performances in mice [1].

However, considering that episodic-like memory seems not to be altered in 3 months-old 5-HT\textsubscript{7} KO mice [2], we hypothesized that a deficit could appear later.

Objectives

To identify the implication of 5-HT\textsubscript{7}R on the onset of the age-related memory decline, memory performances of 7-8, 10-12 and 13-15 months-old KO C57BL/6J mice were compared to paired wild type mice (WT). Recognition memory performances were assessed in a two sessions Y-maze test (1-hour delay [3]). Spatial working memory performances were evaluated by recording spontaneous alternation behavior in the Y-maze apparatus. In addition, locomotor activity was recorded in an activity cage and anxiety-related behavior assessed in the elevated plus-maze test.

Experimental paradigm

- **Object recognition task (Y-maze)**
- **Spatial working memory**
- **Anxiety-related behavior**
- **Locomotor activity**

Spatial working memory

<table>
<thead>
<tr>
<th>Percentage of alternation</th>
<th>WT</th>
<th>KO</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-8 months</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>10-12 months</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>13-15 months</td>
<td>80</td>
<td>80</td>
</tr>
</tbody>
</table>

KO: 7-8m n=5 ; 10-12m n=8 ; 13-15m n=4

Anxiety-related behavior

ELEVATED PLUS-MAZE (EPM)

<table>
<thead>
<tr>
<th>Percentage of time spent in open arms</th>
<th>WT</th>
<th>KO</th>
</tr>
</thead>
<tbody>
<tr>
<td>7-8 months</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>10-12 months</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>13-15 months</td>
<td>50</td>
<td>50</td>
</tr>
</tbody>
</table>

KO: 7-8m n=5 ; 10-12m n=8 ; 13-15m n=4

Locomotor activity

ACTIMETRY (activity cage)

- Both WT and KO mice exhibited an equivalent basal level of locomotion whatever the age.

Conclusions

- Our data show that WT mice older than 10 months-old have episodic-like memory deficits. These ones appear earlier in 5-HT\textsubscript{7}R disrupted mice.
- Likewise, spatial working memory deficits appear around 13 months-old in WT mice, whereas they appear earlier in mutant mice.
- However, KO and WT mice exhibit an equivalent basal level of locomotion.
- Moreover, WT mice seem to present a reduction of anxiety-related behavior at 13-15 months-old, contrary to KO mice.

This suggests that the onset of episodic-like memory decline comes between 7-8 and 10-12 months-old of age in C57BL/6J mice. However, spatial working memory deficits seem to occur later (around 13 months-old) in WT mice. Disruption of 5-HT\textsubscript{7}R could accelerate the onset of both memories decline, with no relation to inhibition of locomotor activity or increased anxiety-related behavior.

References


No potential conflict of interest